Medicinal Chemistry

Chapter 10

DRUGS AFFECTING THE ADRENERGIC SYSTEM

Contents

1. Overview

- the other important player in the peripheral nervous system is the adrenergic system, which makes use of the chemical messengers **adrenaline** and **noradrenaline**.

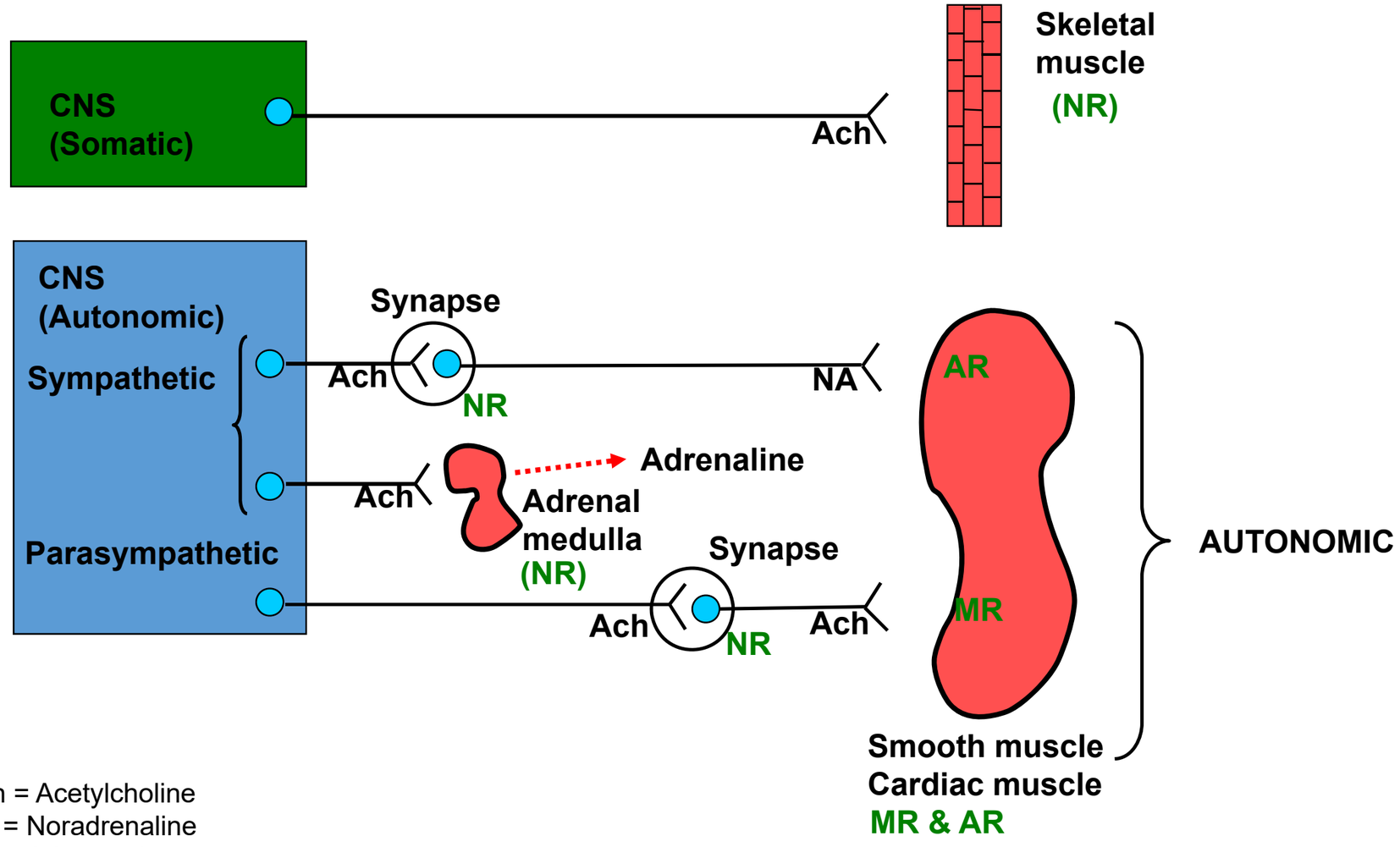
- Noradrenaline "also called norepinephrine" is the **neurotransmitter** released by the sympathetic nerves which feed smooth muscle and cardiac muscle.

- Adrenaline "epinephrine" is a **hormone** released along with noradrenaline from the adrenal medulla and circulates in the blood supply in order to reach adrenergic receptors.

- the adrenergic nervous system has a component of the facility to release adrenaline during times of danger or stress "known **fight or flight** response"

Nerve transmission

Peripheral nervous system



Ach = Acetylcholine
NA = Noradrenaline
AR = Adrenergic receptor
NR = Nicotinic receptor
MR = Muscarinic receptor

1.1 Types of adrenergic receptors

- The main two types of adrenergic receptor are called the α & β- adrenoreceptors and they are G-protein coupled receptors.

- for each type of receptors there are various subtypes with slightly different structures.

- the α receptor consists of α_1 & α_2 with subcategories "α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}". These α receptors produce **inositol triphosphate** "IP3" & **diacylglycerol** "DAG" as secondary messengers.
- The β receptor consists of β_1, β_2, β_3 subtypes and activate the formation of **cyclic-AMP**.
- All these receptor types and subtypes switched on by adrenaline and noradrenaline

2. Distribution of receptors

- certain tissues contain more of one types of adrenoreceptor than another.

- Activation of α-receptors generally **contracts** smooth muscle "except in the gut", whereas activation of β-receptors generally **relax** smooth muscle except in heart muscle causes **contraction** of the muscle and increase the heart rate and force "β1".

- blood vessels supplying skeletal muscle have mainly β2 and are **dilated** by adrenaline, but the blood vessels elsewhere have mainly α- receptors and are **constricted** by adrenaline.

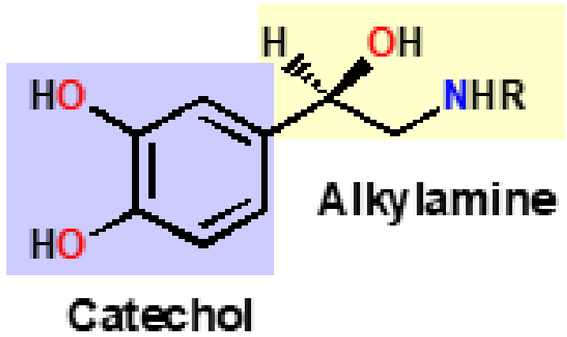
- the overall effect of adrenaline is to increase blood pressure and at the same time provide sufficient blood for the muscles in the "fight or flight response".

Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Heart muscle	β_1	Muscle contraction	Increased heart rate and force
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways
	β_2	Smooth muscle relaxation	Dilates and opens airways
Arteriole smooth muscle (not supplying muscles)	α	Smooth muscle contraction	Constricts arterioles and increases blood pressure (hypertension)
Arteriole smooth muscle (supplying muscle)	β_2	Smooth muscle relaxation	Dilates arterioles and increases blood supply to muscles
Veins	α	Smooth muscle contraction	Constricts veins and increases blood pressure (hypertension)
	β_2	Smooth muscle relaxation	Dilates veins and decreases blood pressure (hypotension)
Liver	α_1 & β_2	Activates enzymes which metabolize glycogen and deactivates enzymes which synthesize glycogen	Breakdown of glycogen to produce glucose
Gastrointestinal tract smooth muscle	α_1, α_2, and β_2	Relaxation	'shuts down' digestion
Kidney	β_2	Increases renin secretion	Increases blood pressure
Fat cells	β_3	Activates enzymes	Fat breakdown

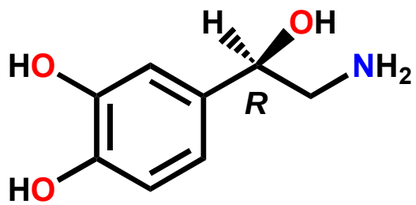
3. Biosynthesis of Noradrenaline & Adrenaline

- Adrenaline and noradrenaline belong to a group of compounds called the catecholamines because they have an alkylamine chain linked to a catechol ring.

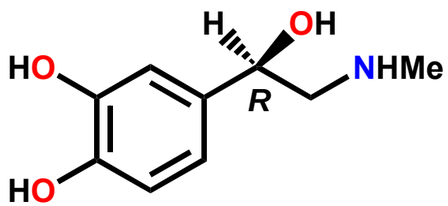
General structure of catecholamines

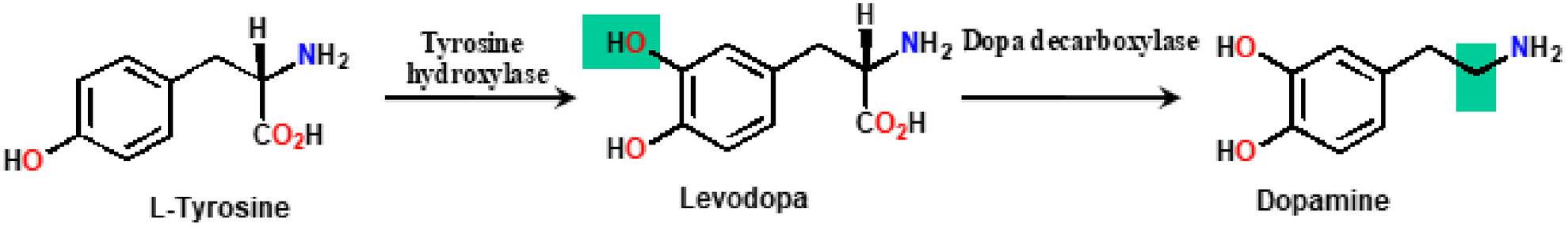


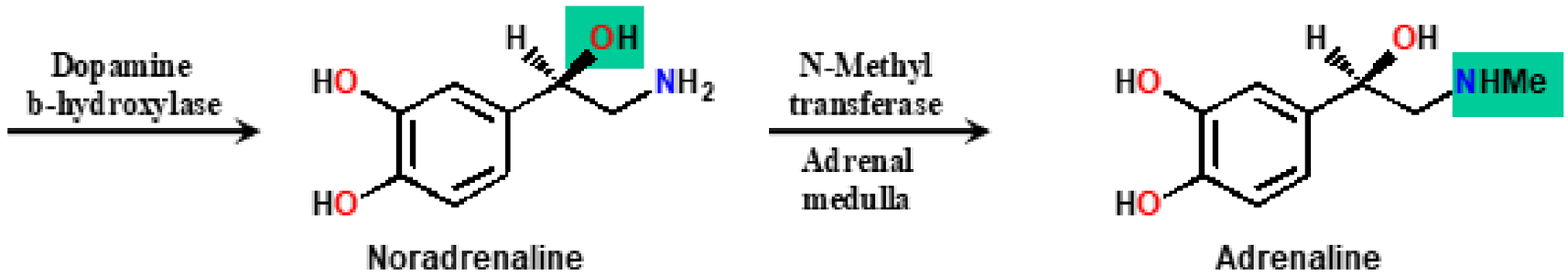
Noradrenaline - neurotransmitter



Adrenaline - hormone



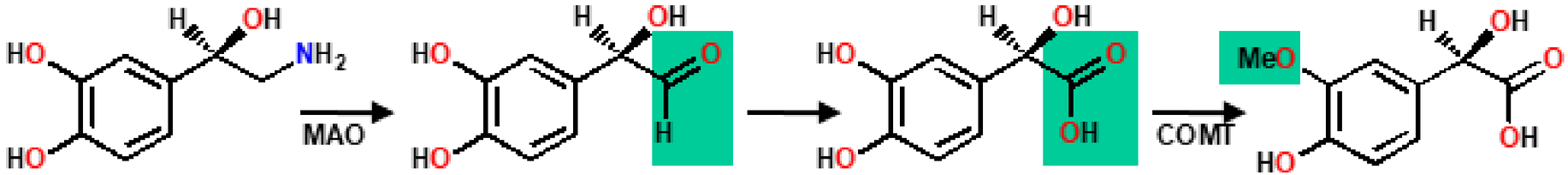

H
NH2
CO2H
HO
L-Tyrosine
Tyrosine
hydroxylase
HO
HO
H
NH2
CO2H
Levodopa
Dopa decarboxylase
HO
HO
NH2
Dopamine


Dopamine
b-hydroxylase
H
OH
HO
HO
NH2
Noradrenaline
N-Methyl
transferase
Adrenal
medulla
H
OH
HO
HO
NHMe
Adrenaline

4. Metabolism of Noradrenaline

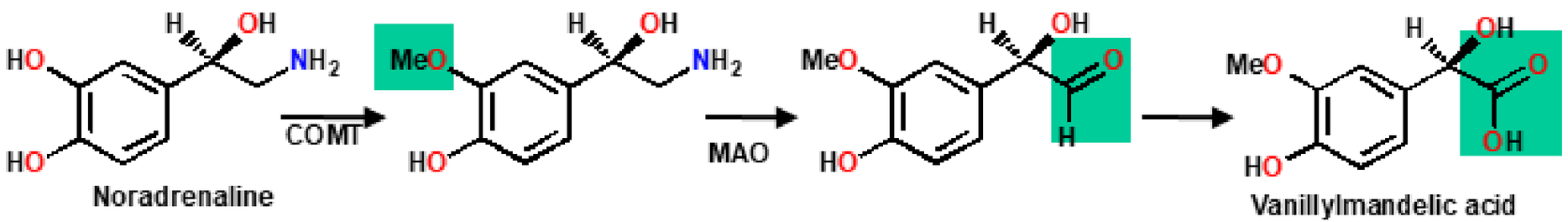
- Metabolism takes place within the cells and involves two enzymes- **monoamine oxidase** "MAO" & **catechol O-methyltransferase** "COMT".

- The final carboxylic acid is polar & excreted in the urine.



Noradrenaline Vanillylmandelic acid

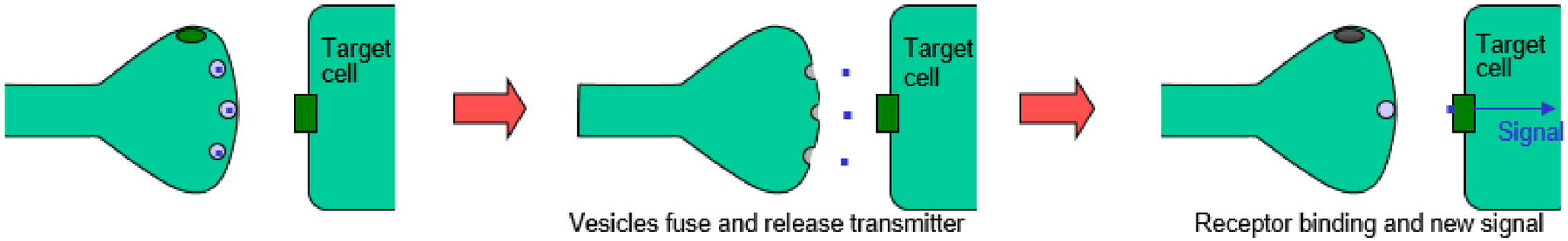
OR



Noradrenaline Vanillylmandelic acid

5. Neurotransmission process

5.1 The neurotransmission process



The neurotransmission process

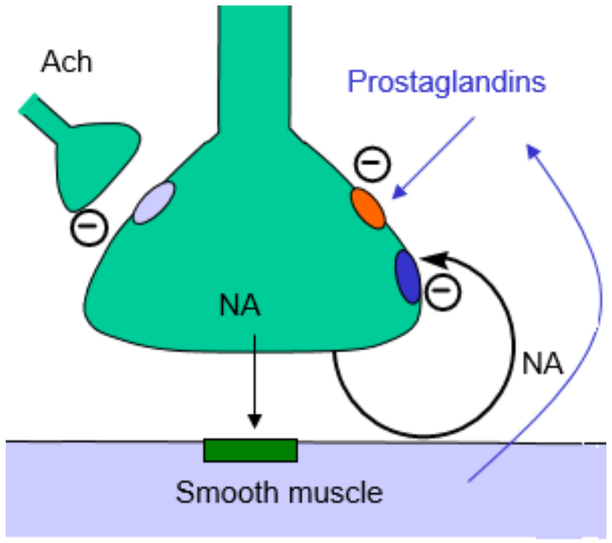
1. Noradrenaline is biosynthesized in a presynaptic neuron then stored in membrane-bound vesicles.
2. When a nerve impulse arrives at the terminus of a neuron, it stimulates the opening of calcium ion channels and promotes the fusion of the vesicles with the cell membrane to release noradrenaline.
3. The neurotransmitter then diffuses to adrenergic receptors on the target cell where it binds and activates the receptor, leading to the signalling process which will eventually result in a cellular response.
4. After the message has been received, noradrenaline departs the receptor and is taken back into the presynaptic neuron by a transport protein.
5. Once in the cell, noradrenaline is repackaged into the vesicles. Some of the noradrenaline is metabolized before it is repackaged, but this is balanced out by noradrenaline biosynthesis.

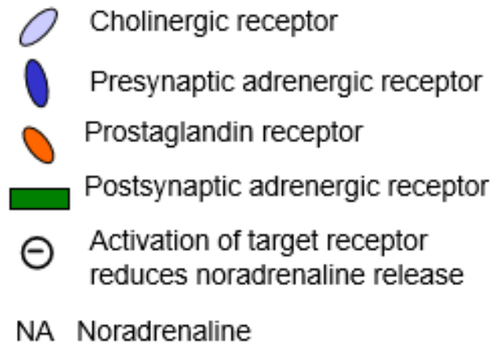
5.2 Co-transmitters

The process of adrenergic neurotransmission is actually more complex. For example, noradrenaline is not the only neurotransmitter released during the process. Adenosine triphosphate (ATP) and a protein called chromogranin A are released from the vesicles along with noradrenaline and act as co-transmitters. They interact with their own specific receptors on the target cell and allow a certain variation in the speed and type of message which the target cell receives. For example, ATP leads to a fast response in smooth muscle contraction.

5.3 Presynaptic receptors and control

- Exist presynaptic receptors which have a controlling effect on noradernaline release.
- There is an adrenergic receptor "α_2-adrenoceptor" which interacts with released noradernaline & has an inhibitory effect on further release of noradrenaline. So it controls its own release by a negative feedback system.
- There are receptors specific for prostaglandins released from target cell to control the release of the adrenergic signals.
- There are presynaptic muscarinic receptors that are specific for acetylcholine and serves to inhibit release of noradrenaline.
- So, when the **cholinergic system is active** it sends **signals along its side branches to inhibit adrenergic transmission**.

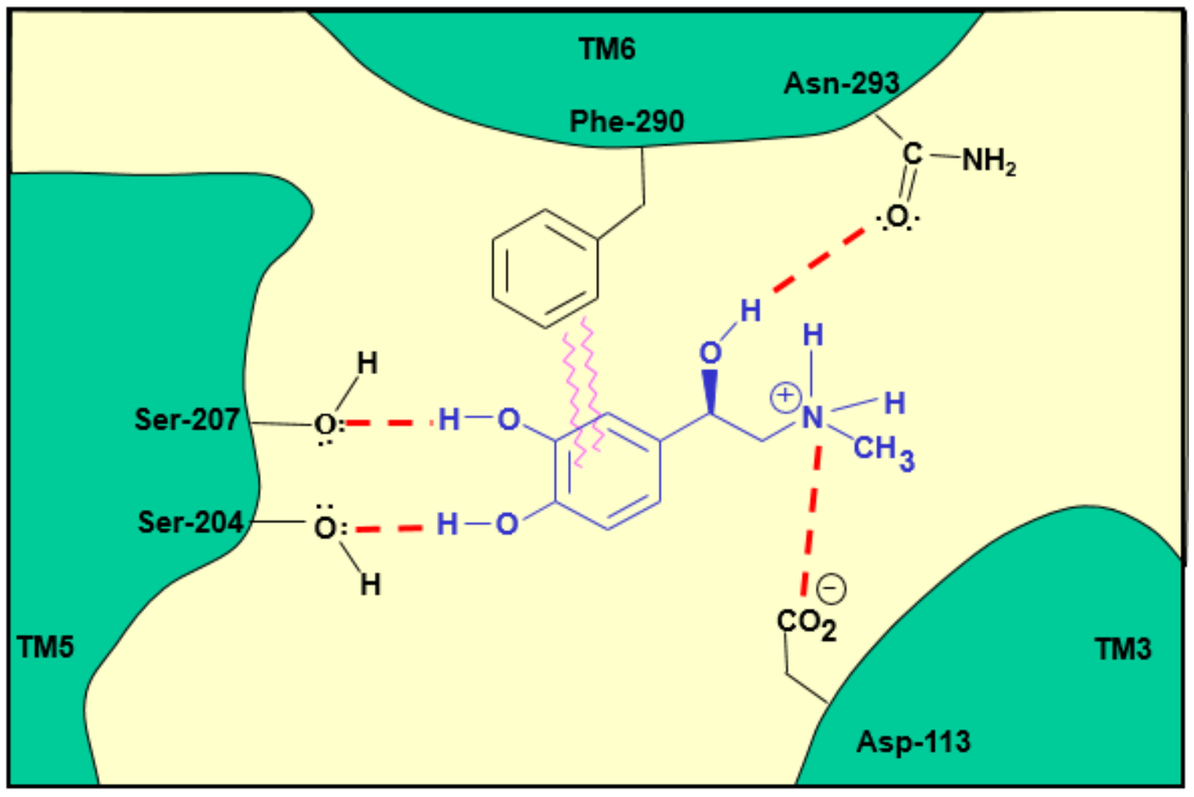




6. Adrenergic binding site

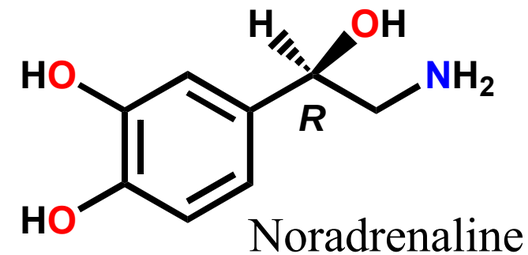
- the molecular modeling and mutagenic studies proposed that three of the seven transmembrane helices “TM3, TM5, & TM6” are involved in the binding site.

- they indicate the importance of an aspartic acid residue “Asp-113”, a phenylalanine residue “Phe-290” and two serine residues “Ser-207 & Ser204”. As we can see in the figure:



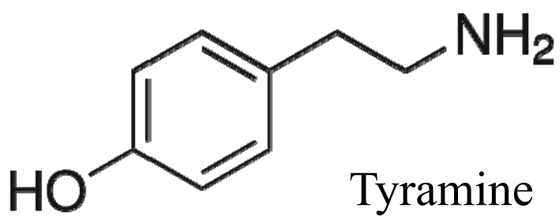
7. Structure-activity relationships

- **Important binding groups on catecholamines**



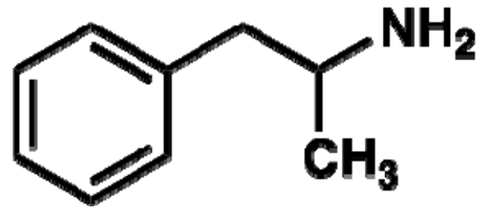
Noradrenaline

- **The alcohol group**: the *R*-enantiomer of noradrenaline is more active than the *S*-enantiomer, indicating that the secondary alcohol is involved in a hydrogen bonding interaction.
- Compounds lacking the hydroxyl group "e.g. dopamine" have a greatly reduced interaction.



Tyramine

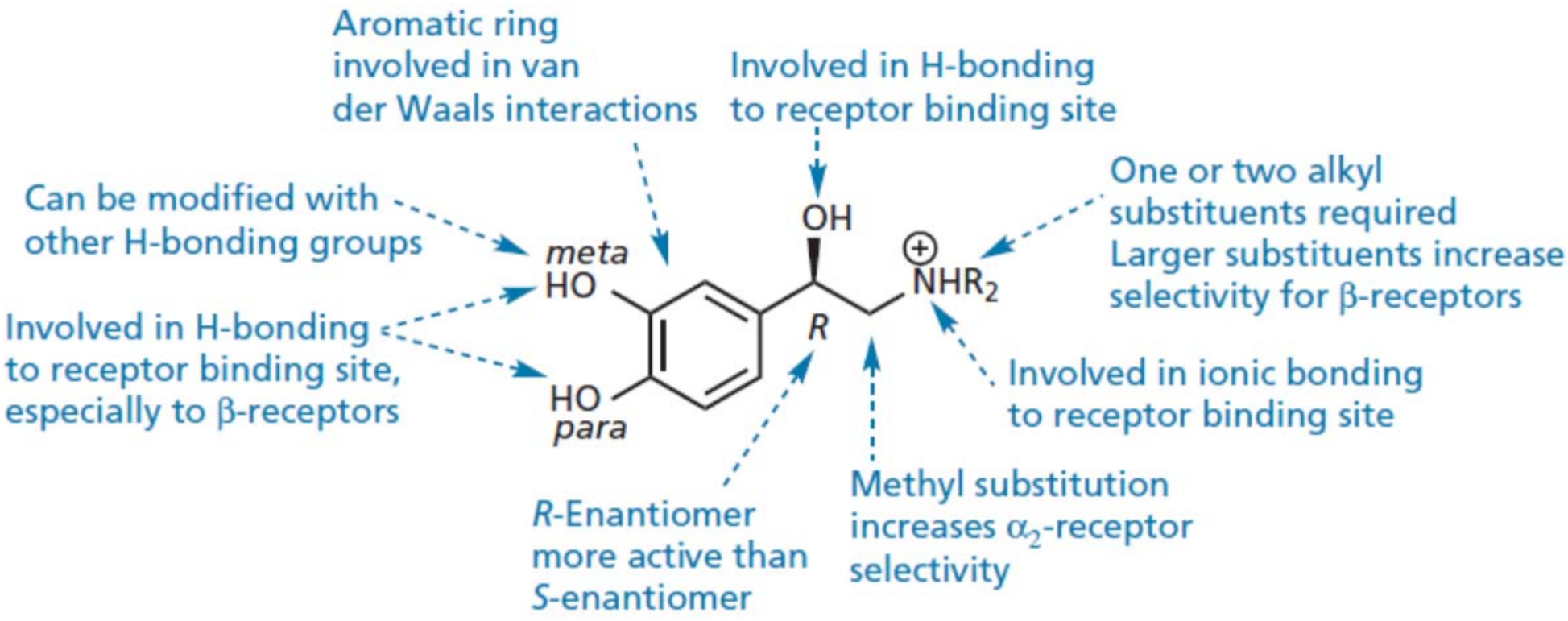
- **The amine**: is normally protonated and ionized at physiological pH. This is important since replacing nitrogen with carbon results in a large drop in activity.
- Activity is also affected by the number of substituents on the nitrogen. 1° and 2° amines have good adrenergic activity, whereas 3° amines and quaternary ammonium salts do not.



Amphetamine

- The phenol substituents: are important, e.g. tyramine & amphetamine have not affinity for adrenoceptors.

➢**Alkyl substituents**: on the side chain linking the aromatic ring to the amine decreases activity at both α & β adrenergic receptors.



8. Selectivity for α- versus β-adrenoceptors

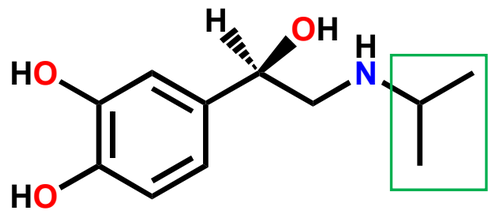
➢SAR studies demonstrate certain features introduce a level of selectivity:

•***N*-Alkyl substitution**: it was discovered that adrenaline has the same potency for both types of adrenoceptors, but noradrenaline has a greater potency for α- receptor than the beta one.

➢Further work demonstrated that increasing the size of the N-alkyl substituent resulted in loss of potency at the α- receptor but an increase in potency at β-receptors.

➢ E.g. **isoprenaline** is a powerful β-stimulant that has isopropyl gp.

These results indicate that the **β-receptor** has a **hydrophobic pocket** into which a bulky alkyl group can fit, whereas the **α- receptor does not.**

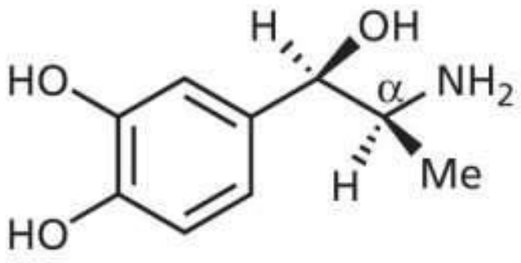


Isoprenaline

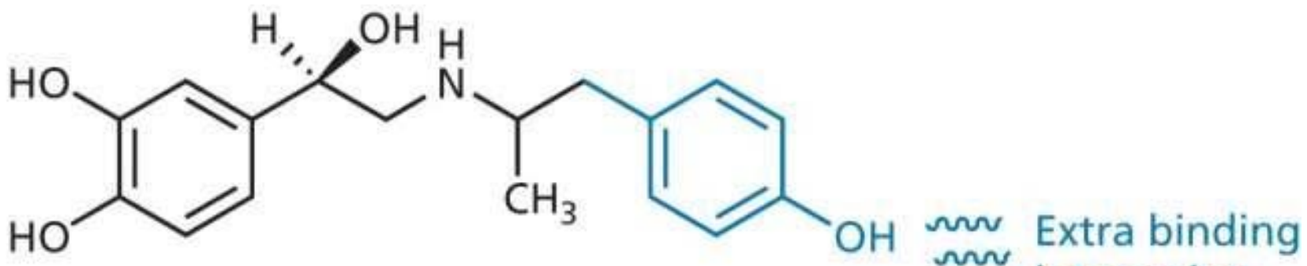
- **Phenol group**: if they are absent, activity drops more significantly for the β-receptors than for the α-receptors. **[absence: β-receptors < α-receptors]**

- **α-Methyl substitution**: addition of an α-methyl group "α- methylnoradrenaline" increases α2-receptor selectivity.

- **Extension:** Increasing the length of the alkyl chain offers no advantage, but if a polar functional gp is placed in particular phenol gp results in a dramatic rise in activity.



α-Methylnoradrenaline



Extension analogue

9. Adrenergic agonists

General adrenergic agonists

- **Adrenaline** itself is an obvious agonist for the overall adrenergic system and it is frequently used in emergency situation such as cardiac arrest or anaphylactic reaction.

- it also administered with local anesthetics to constrict blood vessels and to prolong the local anesthetic activity at the site of injection.

- it is fast acting but it has a short duration and is rapidly cleared from the body. Moreover it switches on all adrenergic receptors.

- this leads to a whole range of side effects including nausea, tachycardia, arrythmias, hypertension, anxiety, tremor, headache.. Etc.

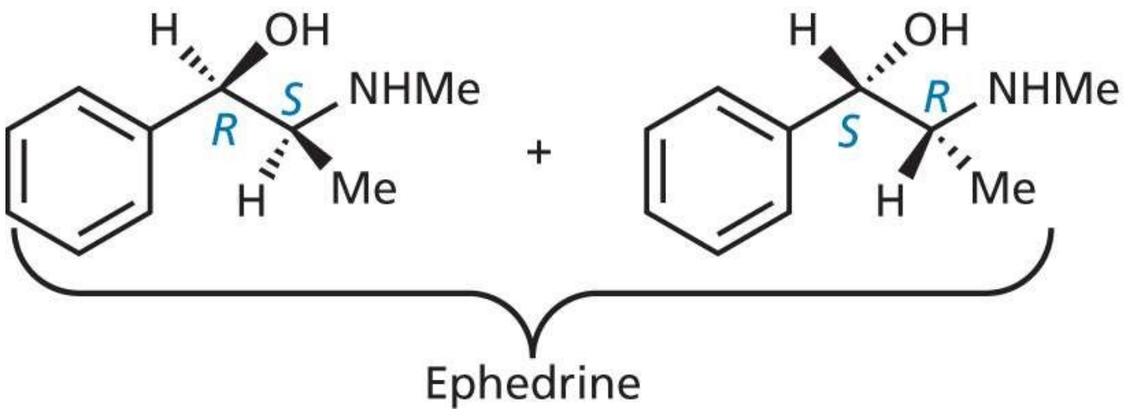
- So, for a long term medication is preferable to have agonists which are selective for specific adrenoceptors.

➢**Ephedrine** is a natural product and have two asymmetric centers so exists as a racemate of the R, S and S, R stereoisomers.

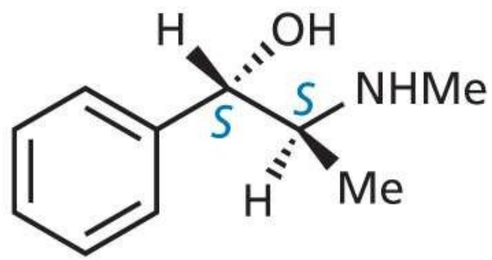
➢it activates both α- & β- receptors and used as bronchodilator. It has also been used as a vasopressor and cardiac stimulant.

➢it lacks phenol group so it does not metabolized by catechol-*O*- methyltransferase, and it can enter the brain because it is highly hydrophobic.

➢**Puesdoephedrine** is also a natural product and is the S,S diasteromer of ephedrine. It is used as a nasal decongestant.



Ephedrine



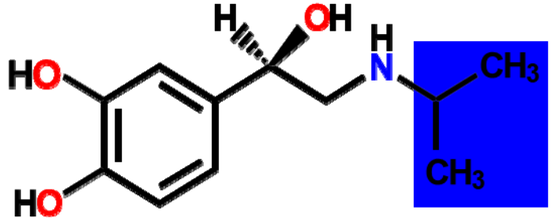
Pseudoephedrine

β_2-agonists and the treatment of asthma

- they can be used to relax smooth muscle in the uterus to delay the premature labour, but they are more commonly used for the treatment of asthma.

- β_2-adrenoceptor predominate in bronchial smooth muscle this leads to dilation of the airways.

➢ **Isoprenaline**:

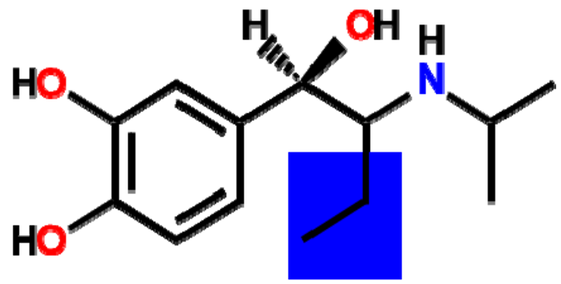


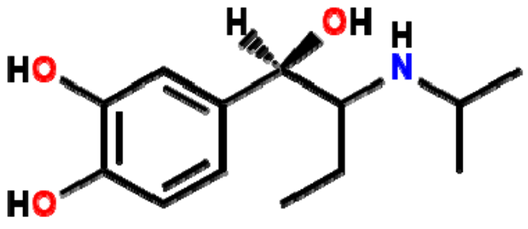
- Isoprenaline is a β-agonist rather than antagonist
- Shows selectivity for b-adrenoceptors
- *N*-Isopropyl group is responsible for selectivity

- Further research demonstrated that selectivity between different types of β-receptors could be obtained by introducing alkyl substituents to the side chain linking aromatic ring and the amine or varying the alkyl substituents on the nitrogen.

➢ **Isoetharine:**

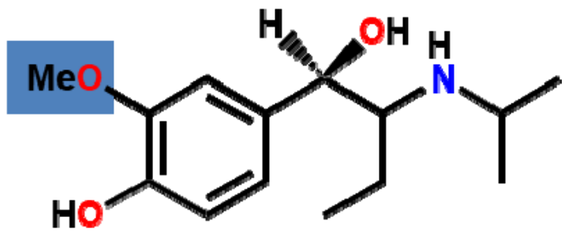
- Shows selectivity for β2-adrenoceptors.
- Ethyl group introduces β2-selectivity.
- Short lasting due to drug metabolism.
- **Metabolised by catechol-*O*-methyltransferase**.





Isoetharine

COMT



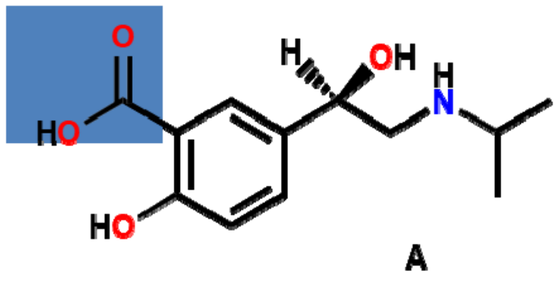
Inactive metabolite

Variation of the *meta*-phenol group

Notes

- Phenol is an important binding group (HBD or HBA)
- Susceptible to metabolism
- Replace with a different hydrogen bonding group

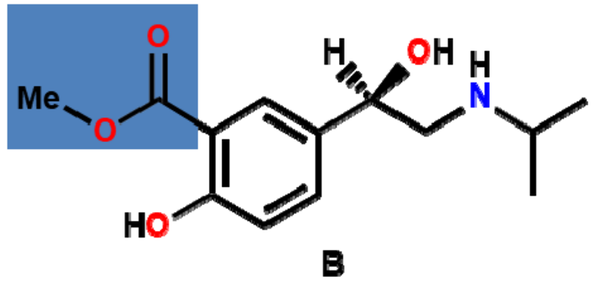
Carboxylic acid



A

Inactive

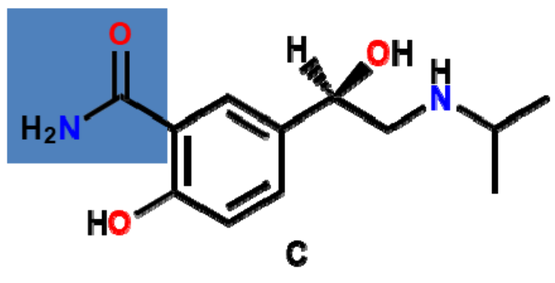
Ester



B

β_2-Antagonist

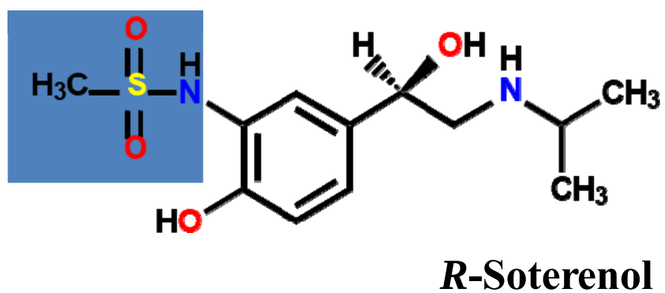
Amide



C

β_2-Antagonist

Sulfonamide

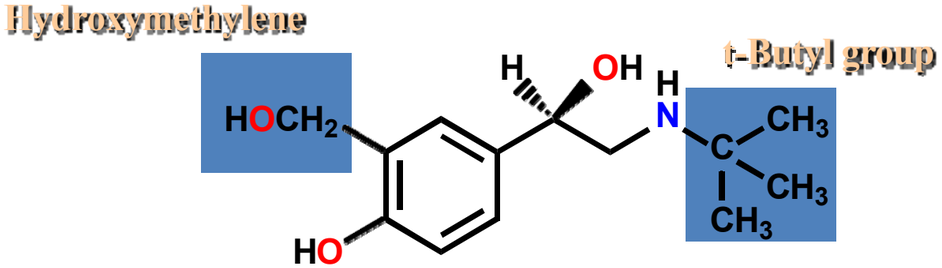


R-Soterenol

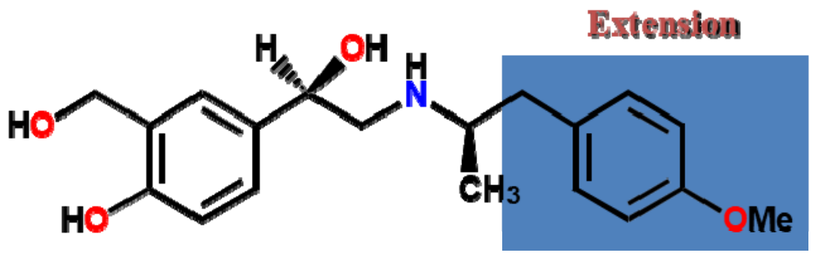
β_2-agonist

❖ Salbutamol (Albuterol)

- Hydroxymethylene group retains β_2-agonist activity
- OH shifted from aromatic ring by one bond length, forms a hydrogen bond to the target receptor (CH_2OH)
- Not recognised by COMT
- Same potency as isoprenaline, but 2000 times less active on the heart
- 4 hours duration of action
- Market leader for the treatment of asthma
- Administered as a racemate by inhalation, the *R* enanotiomer is 68 times more active than the *S* enanotiomer. The *S* accumulates to a greater extent in the body & produces side effects.
- *R* enantiomer is **levalbuterol**, & it is an example of chiral switching.
- Having identified the advantages of a hydroxymethyl group at the meta position, attention turned to the N-alkyl substituents.

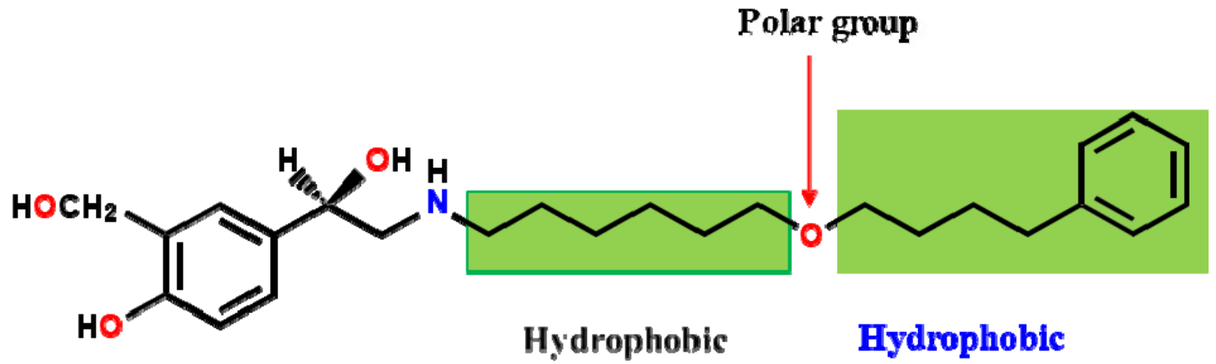


Salmefamol



- *N*-Arylalkyl group added
- Methoxy group interacts with a polar region of the binding site
- Extra binding interaction
- 1.5 times more active than sulbutamol
- Longer duration of action (6 hours)

Salmeterol "Serevent®"



- Longer lasting agent
- Used for nocturnal asthma
- Increased lipophilicity
- Binds more strongly to tissue in vicinity of the receptor
- N-Substituent is lengthened
- 2x more active than salbutamol
- Longer duration of action (12 hours)

10. Adrenergic receptor antagonists

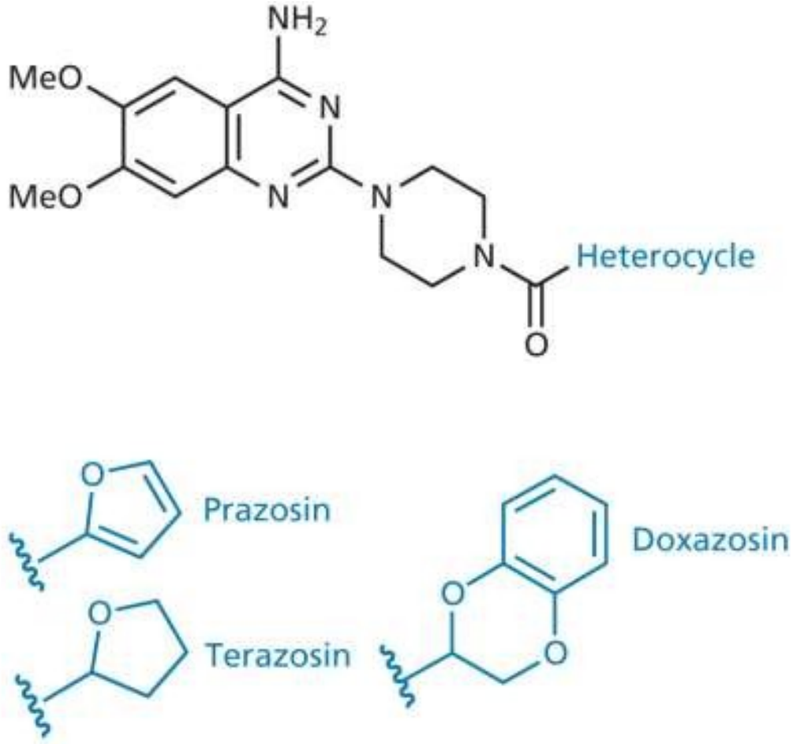
❑ α-Blockers

- they have been limited to selective α_1-antagonists, which have been used to treat hypertension or to control urinary tract.

- **Prazosin** was the first $\underline{\alpha_1\text{-selective}}$ antagonists to be used for the treatment of hypertension, but it is short acting.

- Longer lasting drugs such as **doxazosin** and **terazosin** are better.

- they block the **α1** receptors of smooth muscle in blood vessels. This results in relaxation of the smooth muscle and dilation of the blood vessels leading to a lowering in blood pressure.

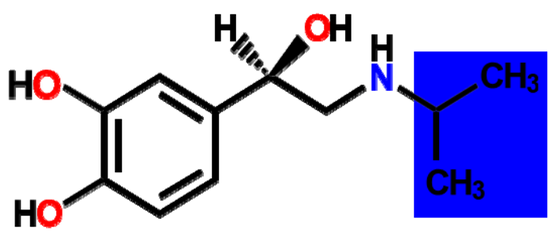


- **Adrenergic antagonists β-Blockers**
- **β -Adrenoceptors**
  - •G-Protein-coupled receptors
  - •Activate generation of cyclic AMP

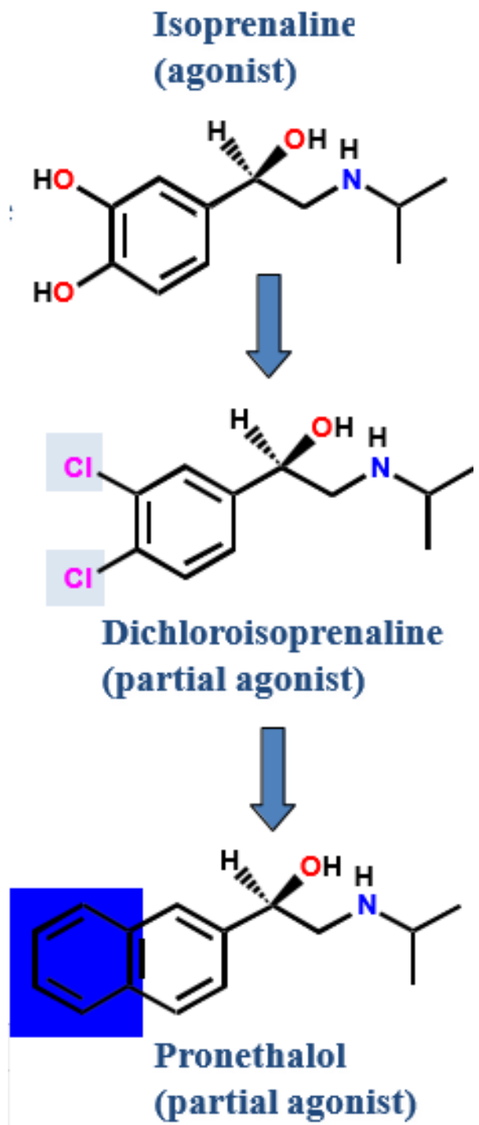
β_3-Adrenoceptor
- •Predominant receptor in fat cells
- •Activation results in fat metabolism

β_2-Adrenoceptor
- •Predominant receptor in bronchial smooth muscle
- •Activation results in smooth muscle relaxation

β_1-Adrenoceptor
- •Predominant receptor in heart muscle
- •Activation results in cardiac muscle contraction
- •Antagonists of this receptor are potential cardiovascular drugs



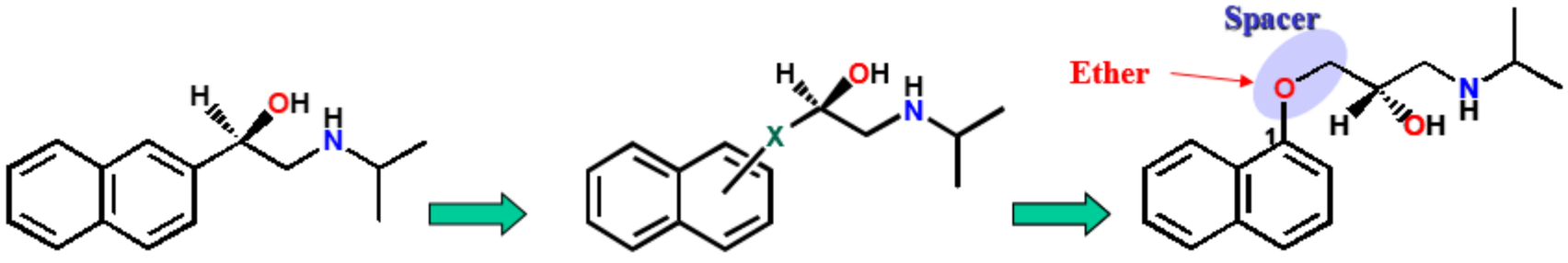
Isoprenaline is a β-agonist rather than antagonist



Converting an agonist to a partial agonist

- Phenol groups are not required for antagonist activity
- Add extra binding groups to convert an agonist to an antagonist
- Hydrophobic groups form extra van der Waals interactions
- Structure binds but produces a different induced fit
- Act as partial agonists
  - weakly activate receptors
  - block natural messenger

Converting an agonist to a partial agonist



Pronethalol
(partial agonist)

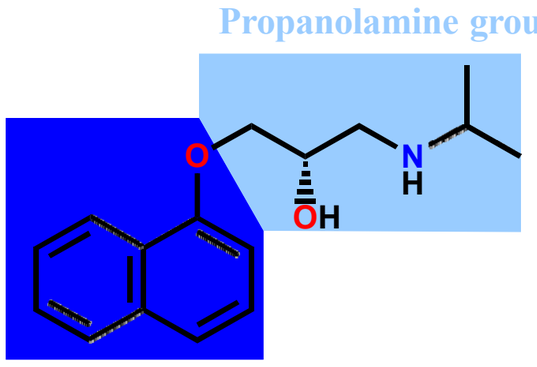
•Introduce spacer
(chain extension)
•Vary substituent position

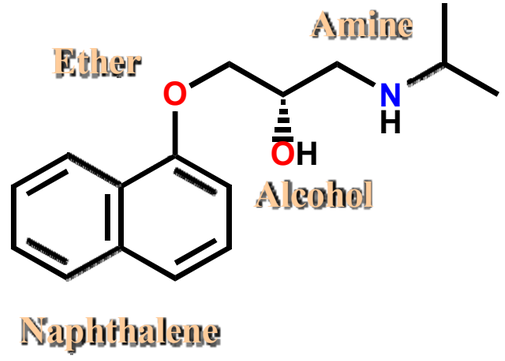
Propranolol
(antagonist)

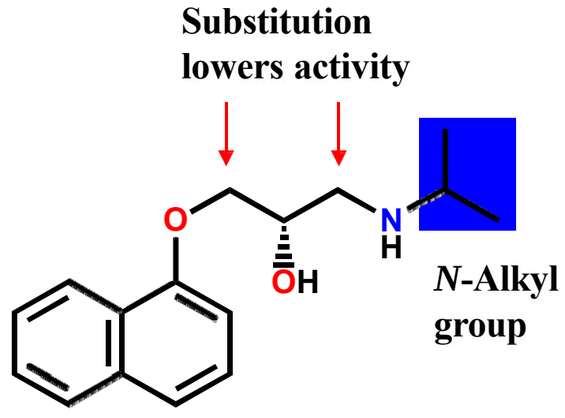
Notes on propranolol

- Spacer introduced - chain extension strategy
- Substituent is positioned at a different part of the ring
- Ether group acts as a hydrogen bond acceptor (extension strategy)
- 10-20 times greater antagonist activity
- Used clinically as a racemate
- *S*-Enantiomer is the active enantiomer
- Aryloxypropanolamine structure
- Activates β_1 and β_2 adrenoceptors

Aryloxypropanolamines



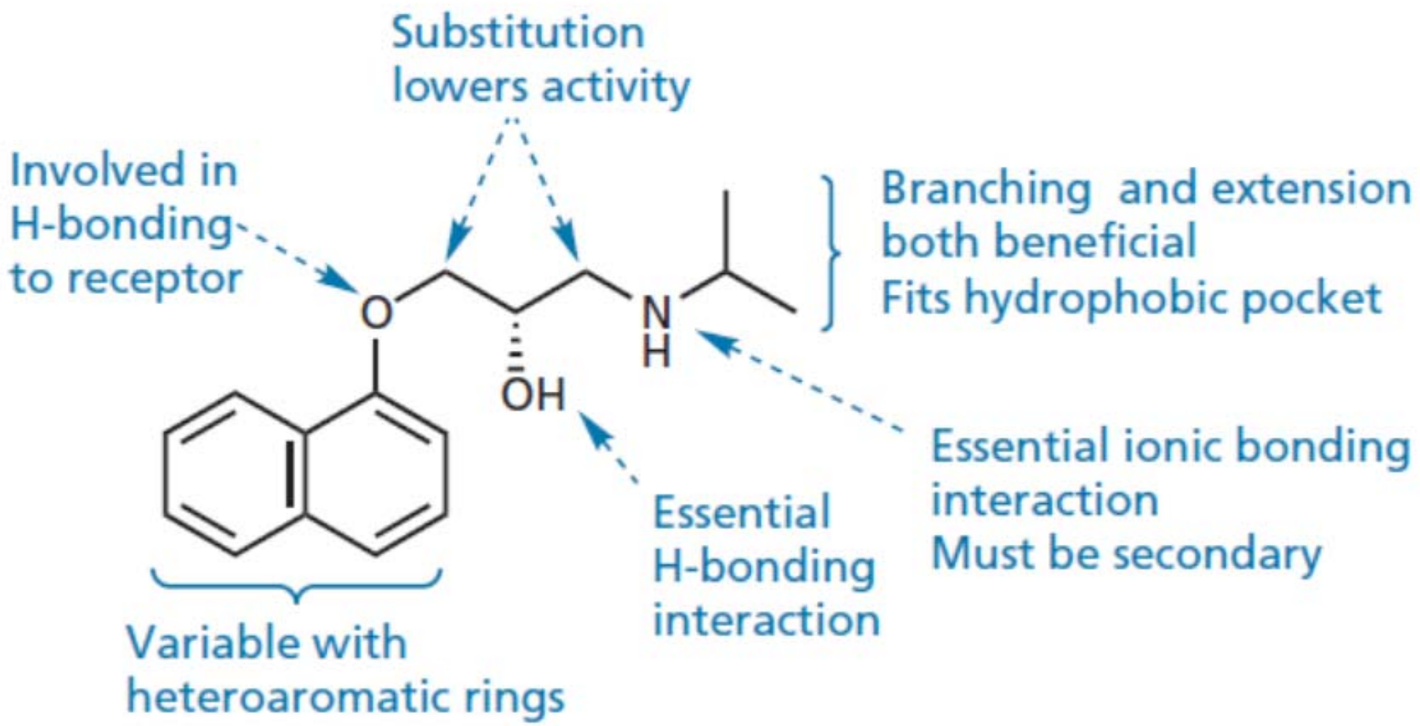




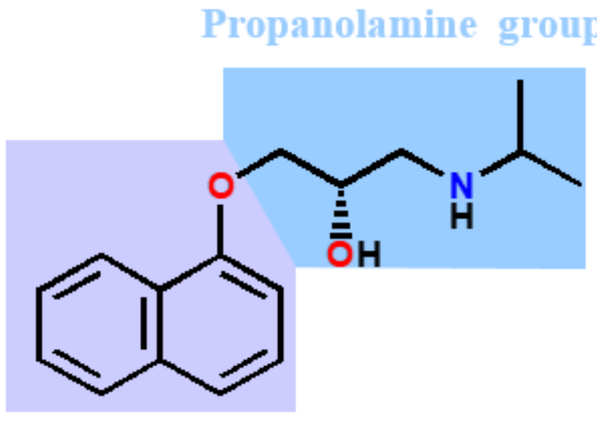
SAR:

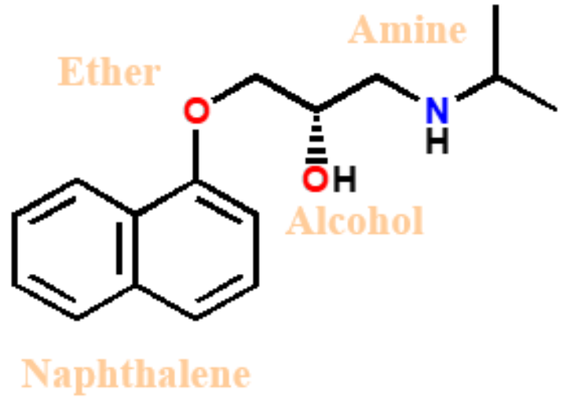
- Ether acts as a hydrogen bond acceptor
- Ether can be replaced with an alternative HBA
- Alcohol is essential as a hydrogen bonding group
- Amine is ionised and forms an ionic bond with the binding site
- Amine must be secondary
- **Naphthalene is replaceable with heteroaromatic rings**
- Branched *N*-alkyl group fits a hydrophobic pocket
- Extension of *N*-alkyl group with *N*-arylethyl group is beneficial

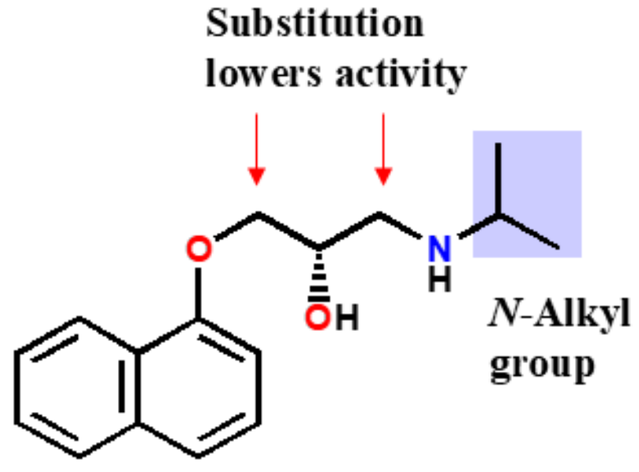
Structure–activity relationships of aryloxypropanolamines



11. Aryloxypropanolamines, 1st generation β-blockers

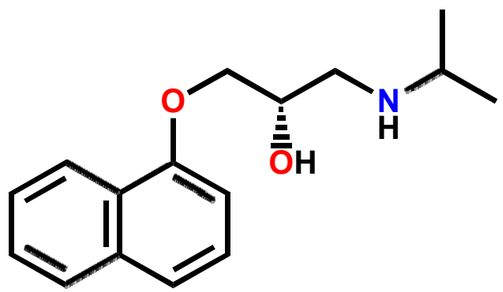




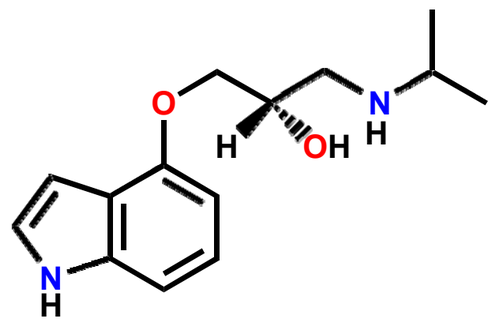


- Ether acts as a hydrogen bond acceptor
- Ether can be replaced with an alternative HBA
- Alcohol is essential as a hydrogen bonding group
- Amine is ionised and forms an ionic bond with the binding site
- Amine must be secondary
- **Naphthalene is replaceable with heteroaromatic rings as Pindolol and Timolol.**
- Branched *N*-alkyl group fits a hydrophobic pocket
- Extension of *N*-alkyl group with *N*-arylethyl group is beneficial

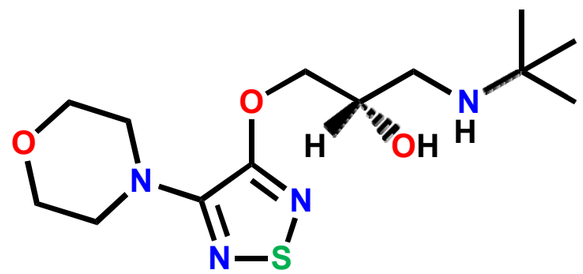
Variation of the naphthalene ring



Propranolol



Pindolol



Timolol

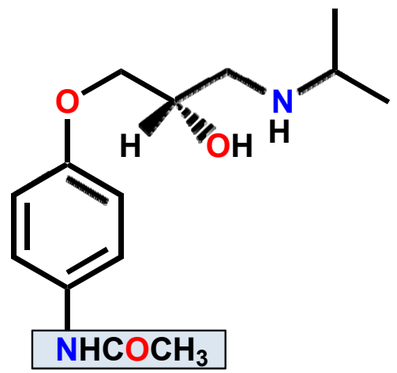
- **Causes less bradycardia than other beta blockers**
- **May cause less coldness of the extremities**

- **Protective value in reducing the recurrence rate of myocardial infarction**
- **Also used in treatment of glaucoma and migraine**

12. Second-generation β-blockers

- **Second-generation β-blockers are designed to be β_1 -selective**

Practolol

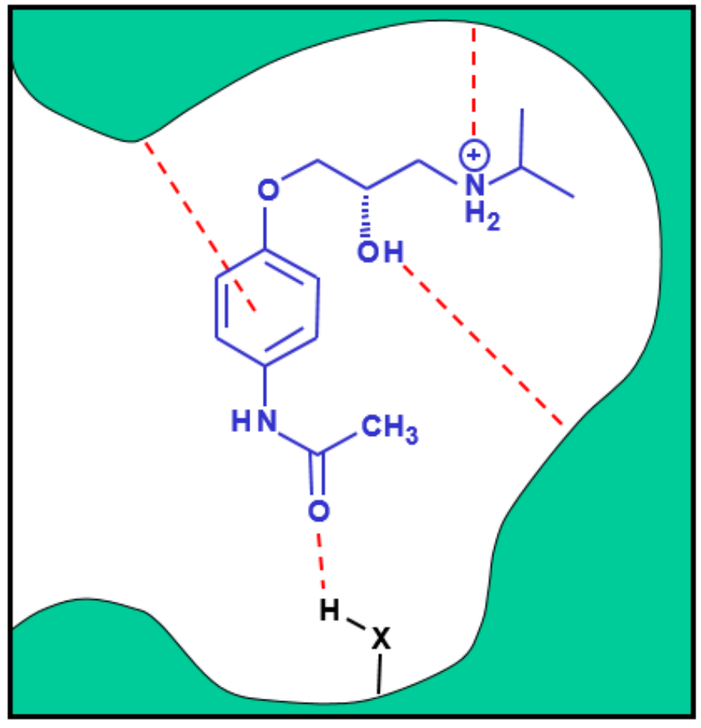


Amide group

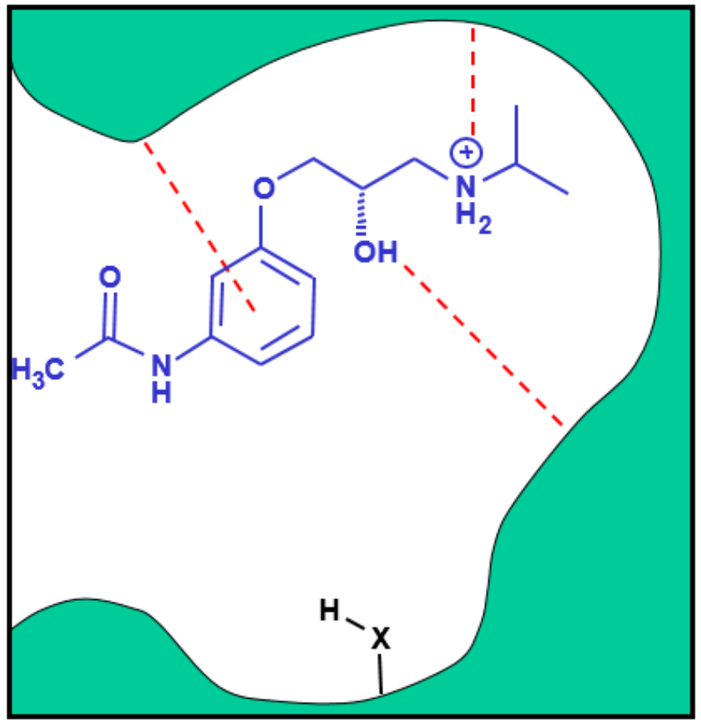
- Selective cardiac β_1-antagonist
- Amide group important for selectivity
- More polar
- Less CNS side effects
- First cardioselective β_1-blocker used for the treatment of angina and hypertension
- Withdrawn due to serious side effects (dry eye syndrome) in some patients

Practolol - binding interactions

- Amido group must be *para* for β_1-selectivity
- Extra hydrogen bonding interaction takes place
- Not possible with β_2-adrenoceptor " because there isn't alkyl substituents to the side chain linking aromatic ring"



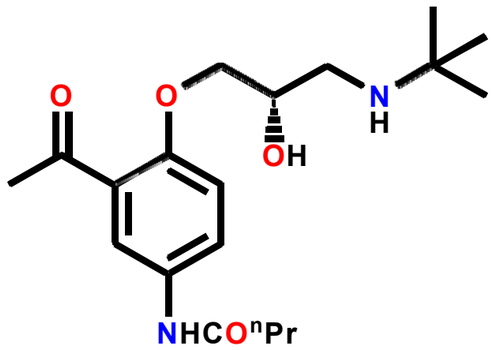
***para* substitution**
Extra H-bonding interaction



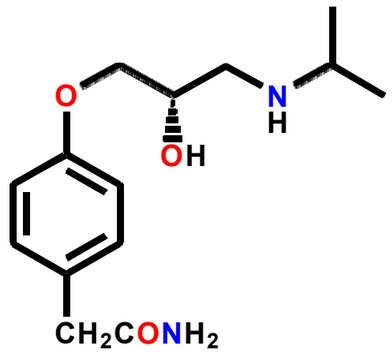
***meta* substitution**

Other agents

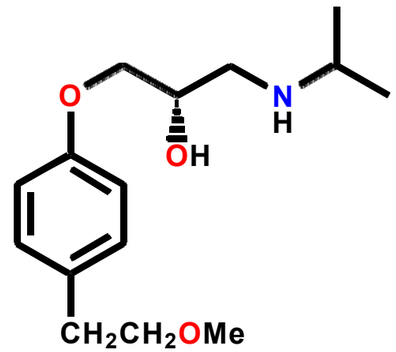
Replacement of the acetamido gp with other groups capable of hydrogen bonding led to a series of cardioselective β1-blockers.



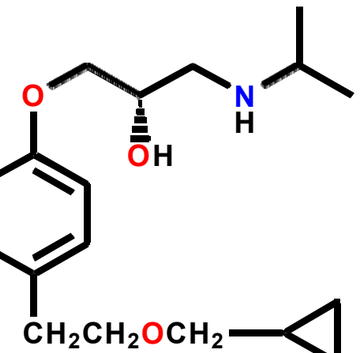
Acebutolol



Atenolol



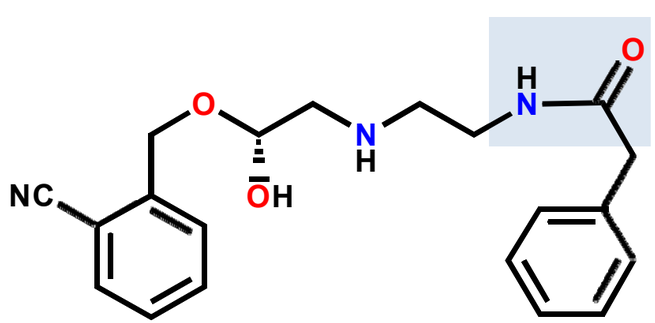
Metoprolol



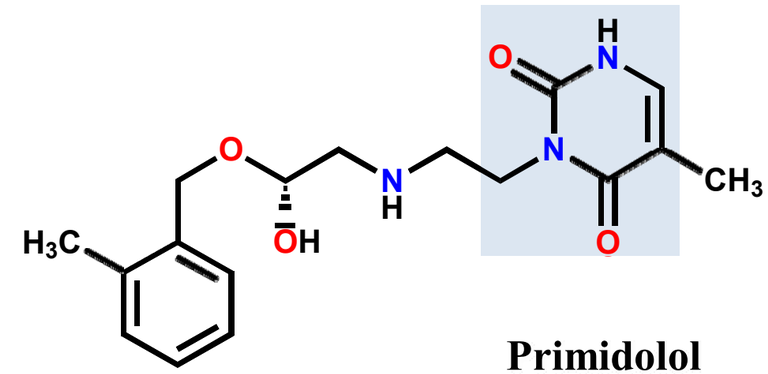
Betaxolol

13. Third-generation β-blockers

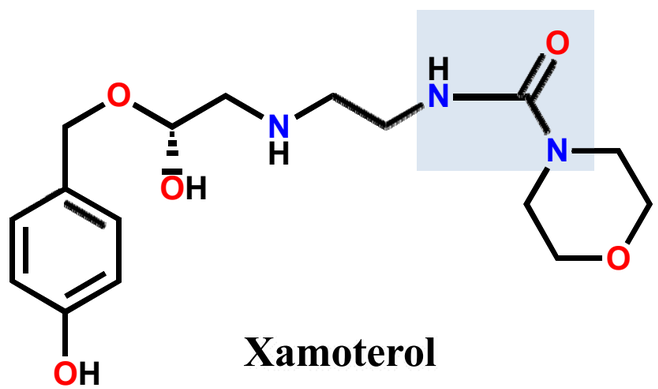
- Includes an *N*-arylalkyl group
- Additional hydrogen bonding interactions are possible
- Extension strategy



Epanolol



Primidolol



Xamoterol

Extra H-bonding interactions